

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
7 April 2005 (07.04.2005)

PCT

(10) International Publication Number
WO 2005/030138 A2

- (51) International Patent Classification⁷: **A61K**
- (21) International Application Number:
PCT/US2004/031478
- (22) International Filing Date:
27 September 2004 (27.09.2004)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/505,922 26 September 2003 (26.09.2003) US
- (71) Applicant (for all designated States except US): **WEBB WARING INSTITUTE** [US/US]; University of Colorado Health Sciences Center, Division of Pulmonary Sciences, 4200 East Ninth Avenue, Box C321, Denver, CO 80262 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **WRIGHT, Richard, M.** [US/US]; 4200 East Ninth Avenue, Box C321, Denver, CO 80262 (US). **REPINE, John, E.** [US/US]; 4200 East Ninth Avenue, Box C321, Denver, CO 80262 (US).
- (74) Agents: **ZISKA, Suzanne, E.** et al.; Morgan, Lewis & Bockius LLP, 1111 Pennsylvania Avenue, NW, Washington, DC 20004 (US).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS OF MODULATING INFLAMMATORY REACTIONS BY MODULATING XANTHINE OXIDOREDUCTASE ACTIVITY

(57) Abstract: Evidence is presented that inflammation and injury involves activation of xanthine oxidoreductase (XOR) in the newly recruited mononuclear phagocytes (MNP). XOR has been shown to be increased predominantly in the MNP that increase rapidly in the lungs of rats that develop acute lung injury (ALI) following intratracheal cytokine insufflation. XOR was recovered from the MNP largely converted to its oxygen radical generating, reversible O-form, and alveolar MNP exhibited increased oxidative stress as evidenced by increased nitrotyrosine staining. Cytokine insufflation also increased alveolar cell apoptosis. A functional role for XOR in cytokine induced inflammation was demonstrated. Tungsten and allopurinol decreased MNP XOR induction, nitrotyrosine staining, inflammatory cell infiltration, and alveolar cell apoptosis. Transfer of control or allopurinol treated MNP into rat lungs, and confirmed a specific role for MNP XOR in promoting lung inflammation. These data indicate that XOR can contribute to lung inflammation by its expression and conversion in a highly mobile inflammatory cell population.



WO 2005/030138 A2